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REVIEW ARTICLE

Unlocking the Benefits of Fasting: A Review of Its Impact on Various Biological Systems and Human Health

Rawan Mackieh[1,#], Nadia Al-Bakkar[2,#], Milena Kfoury[1], Nathalie Okdeh[1], Hervé Pietra[3], Rabih Roufayel[4], Christian Legros[5], Ziad Fajloun[1,6,*] and Jean-Marc Sabatier[7,*]

[1]Department of Biology, Faculty of Sciences, Lebanese University, Campus Michel Slayman Ras Maska, Tripoli 1352, Lebanon; [2]Faculty of Health Sciences, College of Life Sciences, Beirut Arab University, Beirut Campus, P.O.Box 11 50 20, Riad El Solh, 11072809 Beirut, Lebanon; [3]Association Esprit Jeûne & Fasting Spirit, 226, Chemin du Pélican, Toulon 83000, France; [4]College of Engineering and Technology, American University of the Middle East, Kuwait; [5]Univ Angers, INSERM, CNRS, MITOVASC, Team 2 CarMe, SFR ICAT, 49000 Angers, France; [6]Laboratory of Applied Biotechnology (LBA3B), Azm Center for Research in Biotechnology and Its Applications, EDST, Lebanese University, 1300 Tripoli, Lebanon; [7]Aix-Marseille Université, CNRS, INP, Inst Neurophysiopathol, 13385 Marseille, France

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Abstract: Fasting has gained significant attention in recent years for its potential health benefits in various body systems. This review aims to comprehensively examine the effects of fasting on human health, specifically focusing on its impact on different body's physiological systems. The cardiovascular system plays a vital role in maintaining overall health, and fasting has shown promising effects in improving cardiovascular health markers such as blood pressure, cholesterol levels, and triglyceride levels. Additionally, fasting has been suggested to enhance insulin sensitivity, promote weight loss, and improve metabolic health, thus offering potential benefits to individuals with diabetes and metabolic disorders. Furthermore, fasting can boost immune function, reduce inflammation, enhance autophagy, and support the body's defense against infections, cancer, and autoimmune diseases. Fasting has also demonstrated a positive effect on the brain and nervous system. It has been associated with neuroprotective properties, improving cognitive function, and reducing the risk of neurodegenerative diseases, besides the ability of increasing the lifespan. Hence, understanding the potential advantages of fasting can provide valuable insights for individuals and healthcare professionals alike in promoting health and wellbeing. The data presented here may have significant implications for the development of therapeutic approaches and interventions using fasting as a potential preventive and therapeutic strategy.

Keywords: Fasting, cardiovascular system, renin-angiotensin system, immune system, cancer, autophagy, diabetes, nervous system, obesity, COVID-19.

1. INTRODUCTION

Fasting, an age-old practice observed across various cultures and religions, entails voluntarily abstaining from food and/or drink for a defined period. This intentional deprivation has intrigued scientists, health enthusiasts, and medical practitioners alike, leading to burgeoning research exploring the profound impacts of fasting on diverse human body systems. As our understanding of metabolism advances, studies reveal that fasting triggers a range of adaptations within our bodies that extend beyond simple caloric restriction, influencing an array of physiological processes. Fasting encompasses various approaches, including intermittent fasting and prolonged fasting periods, both of which modulate the relationship between nutrient availability and energy metabolism [1]. Beyond the traditional concept of fasting as a means of primary nourishment restriction, researchers have identified several key mechanisms underlying its effects on the human body systems. These mechanisms include cellular autophagy, hormonal regulation, mitochondrial dynamics, and metabolic reprogram-

*Address correspondence to these authors at the Aix-Marseille Université, CNRS, INP, Inst Neurophysiopathol, 13385 Marseille, France; E-mail: sabatier.jm1@gmail.com (J.M.S) and
Laboratory of Applied Biotechnology (LBA3B), Azm Center for Research in Biotechnology and Its Applications, EDST, Lebanese University, 1300 Tripoli, Lebanon; ziad.fajloun@ul.edu.lb (Z.F.)
[#]*These authors contributed equally to this work.*

ming [2-4]. Understanding the importance of fasting transcends the realm of religious or cultural practices; it has emerged as a potential cornerstone for optimizing human health [5]. The ability of fasting to enhance mitochondrial function, promote cellular repair, and regulate cellular homeostasis extensively contributes to its importance [4]. Furthermore, fasting has proven effective in managing various metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular diseases [6, 7]. By delving into the specific benefits fasting offers to each human body system, we ascertain the significance of incorporating fasting regimens into our lifestyles. These metabolic adaptations brought on by fasting have profound implications for weight management, glucose regulation, and overall metabolic health [8]. These impacts open new avenues for potential therapeutic interventions on different body systems, diseases. In this scientific review, we aim to unveil the manifold benefits of fasting on several major human body systems, shedding light on its importance as a potential therapeutic approach.

2. TYPES OF FASTING

Fasting can be done in a number of different ways, ultimately all sharing one aspect: voluntary and temporary abstinence from consuming food and drink. The drive behind this act can range from obesity to health issues to spiritual beliefs. And accordingly, fasting can be divided into different types, which, most, in turn fall into the category of intermittent fasting, defined as an alternation between fasting and eating lasting no more than 24 h [1]. Thus, we divided the different ways of fasting by types:

2.1. Religious Fasting

2.1.1. Christian Fasting

This type of fasting consists of a period of abstinence from all food. However, the eating period also prohibits the consumption of certain foods such as dairy, eggs, meat, fish and alcohol, and, in some cultures, olive oil. This periodic vegetarianism is reminiscent of a Mediterranean-based diet, rich with legumes, nuts, vegetables, olives and seafood [9-11]. According to the Bible, fasting throughout the year is divided into 3 main periods: (i) Advent: 40 days before Christmas. (ii) Great Lent and Holy Week: 48 days before Easter. (iii) The Assumption or Dormition Fast: first 15 days of August. These fasting periods, including additional fasting days such as every Wednesday and Friday, Christmas Eve, Eve of Theophany, among others, add up to a total of 180 to 200 days of fasting out of 365 days, which is, interestingly, nearly 55% of the year, with only four weeks that are “fast-free”, meaning there is no required fasting on Wednesdays and Fridays [9, 10]. Although this type of fasting is followed mainly for spiritual purposes, it could potentially offer many positive physical improvements, which are sadly not well researched. Sarri *et al.*, found that Christian Orthodox fasting made a positive impact on several variables, including a decrease in BMI (Body Mass Index), LDL and Cholesterol, whereas it is the cause of an increase in the consumption of fiber and carbohydrates [9].

2.1.2. Ramadan Fasting

This type of fasting takes place during the holy month of Ramadan, the ninth month of the lunar calendar, and falls under the broader category of Intermittent Fasting (IF) [12]. Individuals choosing to participate in Ramadan fasting abstain from food and drink from dawn until dusk, and the fasting time varies from day to day, and country to country, according to sunset and sunrise times, but generally spans 15 hours a day [12-14]. Each day, individuals consume Suhur, which is the predawn meal preceding a long day of fasting, and break their fast with Iftar, which begins exactly at sunset [15]. This fasting regimen could be quite harsh, especially for people working during the day and unable to sleep away the fasting hours, causing proven cardiovascular strain on workers in physically demanding roles, and especially in times of COVID where wearing protective masks is mandatory, yet have a negative effect on breathing [16]. Some exceptions are therefore made accordingly, notably for pregnant women, people who are traveling, the elderly and those suffering from acute or chronic illnesses, such as diabetes, where fasting could directly negatively impact their health [15].

For those physically able to participate in this difficult fasting period, Ramadan offers many health benefits, additionally to being a spiritually fulfilling experience. The benefits include reduction in body mass, blood pressure, IBD markers (Inflammatory Bowel Syndrome) and Metabolic Disease characteristics such as high fasting blood sugar, elevated triglyceride levels and high blood pressure [12-14].

2.2. Alternate-Day Fasting

Alternate-day fasting is named thus after the method of alternating between fasting days and free eating days. On fasting days, lasting 24 h, fasters consume only 25% of their caloric needs for the day, whereas on feeding days, also extending for 24 h, they are allowed to eat enough to satisfy their appetite, *i.e.*, ad libitum [17]. Thus, people adhering to this protocol fast for 3-4 days out of the week and eat freely for the 3-4 remaining days [18].

It is recommended that fasting does not occur on two consecutive days but rather be spread out to several days of the week, such as Monday, Wednesday and Saturday, and calorie intake be reduced to about 400-600 kcal per day, a very harsh restriction. This energy intake is recommended to be spread out as follows: 30% kcal from fat, 15% kcal from protein, 55% kcal from carbohydrates, and plenty of water should be consumed throughout the day [17, 19] and on feast days, were encouraged to make healthier food choices of low-fat alternatives to dairy and meat [19].

Many positive effects were attained by following this fasting regimen, and most importantly was a decrease in body weight and obesity achieved by adhering to this plan for 4 months or more [19] as well as an improved lipid profile (cholesterol, LDL, *etc.*). In fact, many subjects were able to follow through with this fasting protocol without triggering eating disorder symptoms such as depression, binge eating, fear of obesity, loss of control, emotional eating, and cravings. Subjects also perceived a positive effect on energy levels, psychological wellbeing and a decrease in pain [18, 20].

2.3. Prolonged Fasting

This type of fasting is characterized by a fasting period lasting longer than 24 hours, thus the name "prolonged fasting". This phase can last anywhere from 48 to 120 hours, but phases must be separated by at least a week of normal eating. No specific foods are disallowed, however, participants are only allowed water during their feeding abstinence [21-23]. Prolonged fasting can prove very harsh for a majority of people and can even lead to adverse effects, such as an exacerbation in malnourishment, if already present, and its yet undecided effect on insulin secretion, where some studies rule it out to be detrimental, while others support it as beneficial [22, 24]. During prolonged fasting, and due to a lack of consumption of carbohydrates, insulin secretion subsequently decreases, which reflects poorly on insulin sensitivity, which in turn also decreases. This is an undesired effect for those suffering from diabetes [24]. Following this timeline, glycogen stores are used up, and the body switches to burning fat and ketones to maintain energy needs [21]. As for beneficial effects, this type of fasting promotes a reduction of the size of various organs and tissues, as well as the number of white blood cells and stem-cell-based immune system regeneration. It may also lead to cancer cell death. It can also help cell resistance against toxins and stress. Generally, its effects are more potent than other types of fasting [21, 22].

2.4. Modified Alternate-Day Fasting

Another type of alternate-day fasting, this modified regimen may be applied in various ways, however, most sources agree that it follows a 5:2 rule, meaning that fasting occurs on 2 days of the week, non-consecutively, while the other five days are free-eating days where no food restriction occurs [25, 26]. An additional rule is the absence of complete fasting; instead, it is recommended to restrict calories extremely to reach an intake of 25-50% of the usual recommended calories, *i.e.*, 500 kcal/day for women and 600 kcal/day for men. Consumption of these calories may be distributed across three small meals (extended distribution) or two larger meals (bulking) [25, 27, 28].

Some drawbacks occur naturally, as with any type of extreme fasting, specifically regarding diabetes, as fasting blood sugar was found to be higher than other fasting methods, and the sought after positive effects of regular alternate-day fasting, such as a reduction of growth factors like IGF-1, which are correlated with a decrease in cell proliferation, and therefore are used as markers in cancer research [25, 28].

Some positive points to consider include a decrease in hunger and an increase in fullness reported in people following this fasting method, making adhering to such a fasting protocol more agreeable [25], as well as a general decrease in body weight, observed as a decrease in percentage of visceral fat, with an increase in subcutaneous fat, which translated overall into a much better body fat distribution achieved in a relatively short period of time (~4 weeks) [29].

3. EFFECT OF FASTING ON OBESITY AND DIABETES

Obesity is one of the well-known risk factors for the development of type 2 diabetes. A number of mechanisms are thought to participate in the development of insulin resistance in obese patients. Systemic chronic inflammation and ectopic lipid accumulation are examples of this [30-34]. Otherwise leptin, a hormone secreted by adipocytes, is known to play a functional role in

Table 1. Types of fasting. This table contains the various types of fasting discussed, the method with which to adhere to them, and any special requirements that must be followed.

Type of Fasting		Method	Special Requirements	References
Christian Fasting	Advent	40 days before Christmas	Abstaining from eating dairy, meat*, eggs, fish* and alcohol during feeding time *permitted on certain days	[9-11]
	Great lent + Holy week	48 days before Easter		
	Assumption (Dominian)	First 15 days of August		
Ramadan Fasting		From dusk until dawn during the Holy month of Ramadan	No food or drink restrictions during feeding period No food or water consumption during fasting period	[12-15]
Alternate-Day		24 h fast followed by 24 h of feeding Fasting for 3-4 days of the week	400-600 kcal/day during fasting days. No restrictions during feeding days	[17-19]
Prolonged		48-120 h fasts broken up by a week of normal eating	Only water allowed during fasting period	[21-23]
Modified-Alternate Day		5:2 method: 2 days of fasting interspersed by 5 days of normal eating	No complete fasts, calorie intake reduction to up to 75% of the daily caloric needs	[25-28]

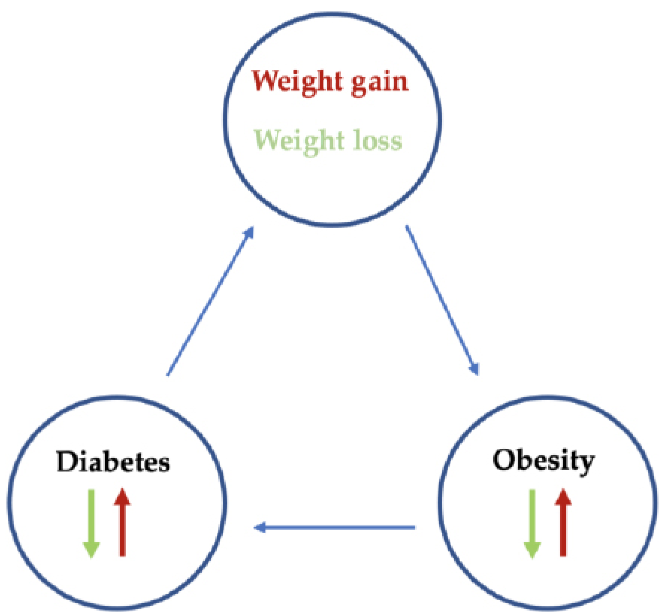

Fig. (1). A scheme illustrating that obesity and diabetes Mellitus Type 2 are dependent on body weight. Created with BioRender.com. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

body weight management by signaling to the hypothalamus and other brain regions to reduce food intake and increase energy expenditure [34]. Remarkably, individuals with higher levels of BMI and insulin resistance were shown to have higher concentrations of leptin, presumably indicating that individuals with obesity and insulin resistance are also developing leptin resistance [35, 36]. So definitely, normal weight is the key to avoid obesity, which contributes to diabetes and many other health problems (such as cardiovascular diseases [37]. All these factors are considered as a closed ring, each factor affects the other (Fig. **1**).

Fasting has emerged as a new lifestyle for losing weight and many studies have shown that most of the weight loss with IF is fat loss [38-46]. In fact, Ramadan fasting is connected with FTO gene, a metabolic gene related to energy metabolism and body fat deposition, and expression downregulation in obese people, which may explain, at least in part, its beneficial metabolic effects. As a result, Ramadan fasting may have a preventive effect against body weight gain and associated negative metabolic-related derangements in obese people [47]. Obese people are three to four times more likely to develop diabetes Type 2 than non-obese people. Obese patients who are suffering from diabetes have found fasting a promising alternative and non-medicinal treatment option for Type 2 Diabetes Mellitus (T2DM), a metabolic disorder characterized by hyperglycemia primarily due to insulin resistance [48]. Interestingly IF showed a decrease in fasting glucose and a positive link between increasing the number of fasting hours and fasting glucose reaching target levels in patients with T2DM [49, 50].

A recent study has established that combining meal timing guidance with prolonged fasting resulted in stronger improvements in postprandial glucose metabolism in persons at high risk of developing type 2 diabetes [51]. Also, a study compared a daily fast of at least 16 hours to calorie restriction in patients with T2DM. Insulin levels decreased in both groups, but IF patients had considerably reduced fasting glucose levels (−0.78 mmol/L *vs* −0.47 mmol/L, $P < 0.05$). The IF group had increased levels of oral glucose insulin sensitivity, lower levels of C-peptide, and lower levels of glucagon. Furthermore, a decrease in hemoglobin A1c (HbA1c) was perceived in T2DM [50, 52, 53]. A randomized control trial was conducted on 3 individuals with T2DM who were followed for several months after starting an IF program of three 24-hour fasts per week. Throughout the study, all patients experienced significant decreases in HbA1C, weight loss, and were able to quit their insulin medication within one month [54]. However, all three patients in this case stated that they tolerated fasting extremely well, and no patient chose to discontinue the intervention at any stage. This shows that IF may not only be effective as a non-medicinal therapy option for patients with T2DM, but also that it is tolerable. An alternate-day fasting regimen was compared to continuous energy restriction. The alternate day fasting group had significant reductions in fasting insulin levels (44%; $p<0.05$) and homeostatic model assessment of insulin resistance (HOMA-IR) levels (53%; $p<0.05$) (marker used to assess insulin resistance) [55]. When compared to the control group, IF resulted in a remarkable decrease in HbA1C and BMI, but statistically insignificant]. More research is needed in this field because T2DM affects 1 in every 11 people. The benefits of IF are obvious, but there isn't enough information to change clinical standards. However, because it works effectively in the long term to reach controlled sugar levels, IF may be utilized as a preventative diet pattern in the pre-diabetic population.

4. EFFECT OF FASTING ON CARDIOVASCULAR SYSTEM

Each year, about 17.9 million people die due to cardiovascular diseases (CVDs), according to WHO [57]. CVDs are a serious issue and should be under control by avoiding any risk factor that makes the chance of death higher, such as smoking, obesity, lack of physical activity, disorders of lipid metabolism, hypertension, diabetes, and poor diet, besides the genetic factors [58, 59]. One of the most effective strategies to prevent cardiovascular events is behavior change. On the one hand, a remarkable number of studies suggest that improving one's diet could significantly reduce the risk of dying from cardiovascular disease [60, 61]. The aim of following a special healthy diet in patients with CVDs is to lower the body mass and reduce the calories, which will consequently reduce the risk of death. Recently, fasting has been followed by many people around the world to reach their target and to follow a diet with a restricted amount of calories. IF is becoming increasingly popular for preventing many CVDs. The holy month of Ramadan is an example of IF, and fasting during this month causes a number of physiological changes that help the body maintain healthy metabolic homeostasis. Naz *et al.* suggested that fasting throughout Ramadan is another non-pharmacologic way to lower CV risk factors [62]. Another study has shown the effect of Ramadan fasting on lipid profile and cardiovascular risk factors in patients with stable coronary heart disease. The results of this study had demonstrated that when compared to their before Ramadan values, levels of apoprotein A, low-density lipoprotein-cholesterol, triglycerides, and cholesterol were all significantly ameliorated after Ramadan fasting. As well as, the blood glucose fasting and CRP levels have considerably reduced [63]. Similarly, the people who practice fasting in Ramadan showed improving in HDL, LDL, triglycerides and very low-density lipoprotein levels with a reduction of Framingham risk score in average 13.8 to 10.8 [64]. On another hand IF helped in lowering blood pressure and this was confirmed in many studies. Following a few weeks of observation in rats which are under IF program, a drop in systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as a decrease in heart rate were observed [65]. Similarly, another study in humans has demonstrated that groups of people who fasted for an extended period of time had lower SBP and DBP [66]. In addition, fasting during Ramadan has improved peripheral and central blood pressure management in both chronic renal disease and hypertensive patients. Also, it is linked to better arterial compliance in hypertensive patients without chronic kidney disease [67]. In the same manner, Ramadan IF lowers heart stress in hypertension individuals who are under the control of their medication regimen, without changing their hypertensive status [68]. A study was conducted on a small sample of prediabetic participants and showed that SBP decreased by 11 ± 4 mmHg as well as DBP reduction of 10 ± 4 mmgHg after 5 weeks of IF for 18-hour periods [69]. Similar to this, prospective observational research of 82 Muslim participants who were followed during Ramadan found a 3-point decrease in systolic blood pressure, but a diastolic change was not statistically significant [64].

Atherosclerosis, a chronic inflammatory disease, is the most common cause of vascular disease worldwide. It shows up clinically in ischemic stroke, peripheral artery disease, and ischemic heart disease. Thus, it is the reason behind acute myocardial infarction, cerebrovascular incidents, and the majority of cardiovascular-related deaths in the world [70, 71]. The formation of atherosclerotic plaque is promoted by pro-inflammatory markers such as homocysteine, interleukin 6 (IL6), or C reactive protein (CRP). A previous study has shown that following a prolonged IF in a model like the month of Ramadan has decreased these pro-inflammatory factors in the fasting group with no changes in the non-fasting group [72]. Lower levels of inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1b, interleukin-6, and interleukin-8, which are thought to have a role in the development of atherosclerosis, have been linked to higher vagal activity [73]. Also, another study has demonstrated that IF has increased the concentration of adiponectin, a biomarker of atherosclerosis, which normally decreases in patients having this disease [74]. It is known that prediabetic patients have a higher chance of developing CVD and microvascular and macrovascular complications. In a recent study, prediabetic patients who followed IF combined with a low-carbohydrate diet (L-CD) have less common microvascular and macrovascular issues [75]. Furthermore, a study has been conducted on people during their two-third of lifespan (mean age 64 ± 14 years) who followed a routine fasting. This routine has shown that fasters have higher survival after cardiac catheterization and a lower incidence of heart failure in comparison with non-fasters [76]. However, previous findings imply that long-term time -restricted eating in conjunction with a resistance exercise regimen is possible, secure, and efficient in lowering inflammatory markers and risk factors for cardiovascular and metabolic conditions [77].

As we mentioned before about obesity and how it affects the body negatively by provoking many health problems it could be an important reason to induce cardiovascular issues [7]. Thus fasting triggers weight loss which will prevent cardiovascular diseases [27, 74, 78-80]. The main benefits of fasting on the cardiovascular system are highlighted in Fig. (**2**).

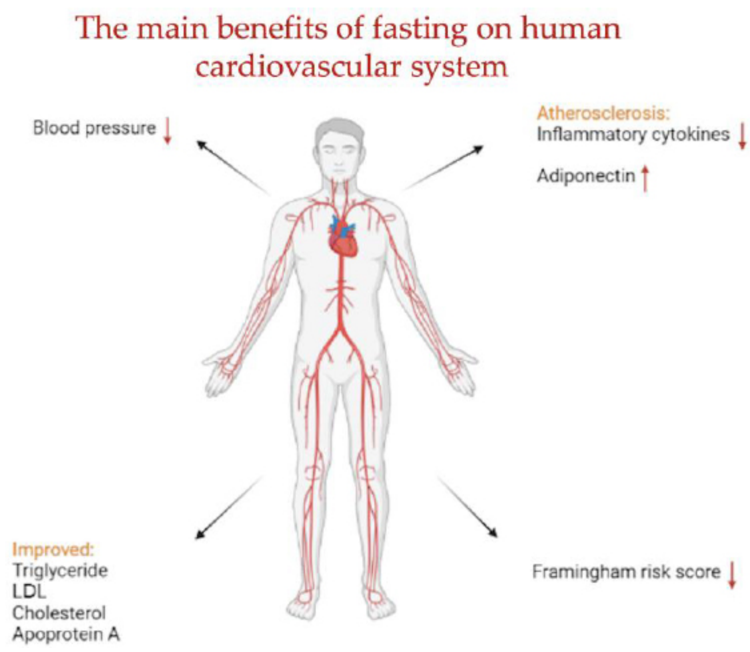

Fig. (2). The impact of fasting on the cardiovascular system. Created with BioRender.com. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5. EFFECT OF FASTING ON RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is a vital physiological system that regulates blood pressure and fluid balance in the body. It plays a crucial role in maintaining homeostasis and is involved in various physiological processes. The importance of the renin-angiotensin system includes (i) blood pressure regulation by controlling the constriction and relaxation of blood vessels, (ii) fluid and electrolyte balance in the body, (iii) maintaining normal kidney function. But for some reasons, blocking the RAS may have some benefits. Starting from hypertension management, heart failure treatment, kidney disease management, and diabetic nephropathy prevention. Usually, blocking the RAS is made through the use of medications like ACE inhibitors or angiotensin receptor blockers (ARBs), but fasting has also been shown to be a blocker of this system. It's well known that obesity has many side effects, such as hypertension, diabetes, *etc.* Obesity is one of the cases in which blocking RAS will be effective in reducing blood pressure and managing the glucose level in the blood in fatty patients. This statement is proved by a previous study conducted on mice that were following a high-fat diet or high-fructose diet for 8 weeks and then subjected to IF protocol showed that the major weight loss caused by the IF treatment resulted in regulation of the local RAS, with further benefit of left ventricle remodeling and blood pressure lowering [81]. The older people get, the higher the chance of developing cardio-vascular disease [82]. In this manner, IF has pointed out in aged rats the capability of recovering the cardiovascular system by restoration of the renin-angiotensin system balance [83]. Also, following an IF protocol displayed an improvement in blood pressure and the association of blood pressure with favorable outcomes such as heart rate variability (HRV), angiotensin-converting enzyme (ACE) activity, and angiotensin II (Ang-II) levels following the IF procedure [84].

6. EFFECT OF FASTING ON IMMUNE SYSTEM

Fasting has shown to affect the immune system on several levels (Fig. **3**). It has been shown to help the immune system function better by lowering inflammation, and reducing oxidative stress [85]. IF strategy has been found to lower inflammation and has been predicted to positively alter the inflammatory state. This is proved by a previous study in which fasting from dawn to sunset (Ramadan fasting) has been demonstrated to improve immune system function by reducing chronic inflammation and oxidative stress, enhancing metabolic profile, and remodeling the gut flora [86]. Furthermore, another study has been conducted on asthma patients and showed that following an alternate day fasting has led to improvement of symptoms, pulmonary function, oxidative stress and inflammation. This could be explained by significantly lowered inflammatory markers such as serum tumor necrosis factor and brain-derived neurotrophic factor (BDNF) [87]. Similarly, a decrease in pro-inflammatory cytokines IL-1β, IL-6, and tumor necrosis factor α (TNF-α) was perceived in healthy subjects who practiced Ramadan fasting also, the immune cells were reduced considerably during Ramadan but remained within normal levels [88]. Remarkably, short and long IF were shown to dramatically reduce inflammatory indicators such as IL-6 and C-reactive protein. Another randomized control trial has demonstrated that time-restricted feeding (TR-F) is a way to prevent inflammation as it causes the decrease of natural killer cells (NK). Also TRF reduces hematocrit, white blood cells, and neutrophils. Interestingly, in this study, TRF does not affect the performance of muscles in young and elderly men [89]. In addition, Mindikoglu *et al.* claimed that IF from dawn to sunset for 30 days can reduce inflammation and improve immunological function [90]. More studies have found that fasting during Ramadan increases the expression of antioxidant and anti-inflammatory genes in both nondiabetic obese individuals and healthy subjects [91, 92]. This anti-inflammatory property of fasting could help in improving inflammatory diseases like inflammatory bowel disease (IBD). In agreement with Song *et al.*, in the mouse model of IBD, treatment with fasting-mimicking diet can effectively alleviate symptoms and pathogenesis of IBD by lowering inflammation marker NLRP3, intestine inflammation, and the percentage of CD4+ T cells along with boosting the regeneration and repair of damaged intestinal epithelium [93]. These data show that IF reduces the inflammatory status of the body by decreasing pro-inflammatory cytokine expression and circulating leukocyte levels without impairing the immune response.

On another hand Ramadan fasting has been shown to enhance macrophage counts while decreasing bacterial levels in the body. Furthermore, this study found that RFP can boost interferon-gamma (IFN-γ), which activates antimicrobial systems in the body [94].

A recent study showed that IF regulates monocyte lifespan, with implications for the ability to adapt to external stressors [95]. In other words, monocytes re-enter the bone marrow during the fasting period, this reentry is directed by hypothalamic-pituitary-adrenal (H-PA) axis-dependent release of corticosterone. However the bone marrow is considered a secure place for monocytes during lack of nutrients. Resulting in a rush of

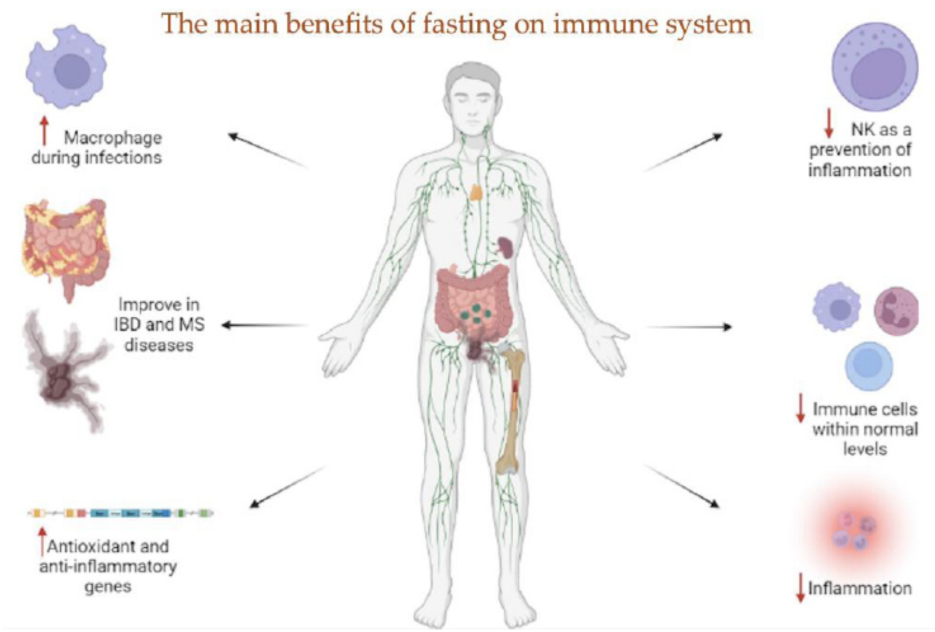

Fig. (3). The impact of fasting on the immune system. Created with BioRender.com. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

monocytes into circulation after re-feeding period [95]. This explains why the number of circulating monocytes is reduced during fasting in humans and mice [96]. Thus monocytes and other immune cells like naive B cells and memory CD8+ T cells take the bone marrow as a haven during fasting period (energy reduction period) to sustain systemic immune-responsiveness [96, 97].

Cycles of prolonged fasting, in particular, not only prevent immune system damage but also stimulate immune system regeneration. This is accomplished by transforming latent stem cells into self-renewing cells, resulting in the production of new blood and immune systems [21]. The process is performed by eliminating older and damaged immune cells and creating new ones, which has consequences for chemotherapy tolerance as well as people suffering from immune system deficits such as autoimmune disorders [21]. This same study explained that during prolonged fasting, the body attempts to conserve energy by recycling a large number of immune cells that are no longer essential, particularly those that are damaged. This causes a decrease in the number of white blood cells. When you re-feed after fasting, your blood cells regenerate, which is a way of enhancing stem cell-based hematopoietic system regeneration. Prolonged fasting additionally triggers the body to use up its stores of glucose, fat, and ketones, as well as break down a major amount of white blood cells. This decrease in white blood cell count causes modifications that stimulate stem cell-based regeneration of new immune system cells [21].

Fasting shows great promise in decreasing the incidence and severity of autoimmune conditions. Multiple sclerosis (MS) affects 2.5 million people worldwide, it is an inflammatory demyelinating disease of the central nervous system (CNS) characterized by different degrees of axon and neuron damage caused apparently by autoimmune processes. In the experimental autoimmune encephalomyelitis (EAE) MS model, IF improved the clinical course and pathology [98]. This happened because IF boosted the diversity of gut bacteria, enriched the Lactobacillaceae, Bacteroidaceae, and Prevotellaceae families, and improved antioxidative microbial metabolic pathways. It's known that By modulating T cell development and immunological responses in the gut, commensal bacteria and their metabolites have the capacity to exert both pro- and anti-inflammatory responses [99]. Also T cells in the gut were altered by IF, with a decrease in IL-17 generating T cells and an increase in regulatory T cells [98]. To add more, intermittent calorie restriction was linked to a decrease in memory T cell subsets in persons with MS [100]. In contrast, a study conducted by Hong *et al.* has shown that IF has a negative effect in mice suffering from lupus nephritis by increasing B cell activation, autoantibody production, lupus nephritis severity and autoantibody immune complex formation in comparison with the control group [101].

7. EFFECT OF FASTING ON CANCER

In 2020, 19.3 million people were affected by cancer, causing the death of around 10 million people worldwide [102]. Cancer is characterized by uncontrolled cell proliferation and has become the most devastating disease, causing increased morbidity and mortality worldwide. Numerous cancer treatments were developed and are considered today as standard therapies, like surgical tumor removal, radiation, chemotherapy, and immunotherapy [102, 103]. But patients who receive these types of treatments must deal with a variety of side effects and the possibility of sickness recurrence, which has an impact on patients on many levels: physically, emotionally, cognitively, financially, and socially. So finding new treatments with no or fewer side effects is needed, and new research reveals that IF might help in the prevention and treatment of cancer by increasing the effectiveness and tolerability of anticancer medications and enhancing the quality of life for cancer patients through a variety of underlying biological mechanisms brought on by IF.

A previous study was conducted on cancer patients including 10 patients (with multiple types of cancer comprising lung, ovarian, breast, uterus, oesophageal and prostate cancer) who fasted for up to 140 hours before and/or up to 56 hours after chemotherapy. Fortunately, no significant side effects were perceived by fasting, except for hunger and lightheadedness. Six patients who had chemotherapy with and without fasting reported a significant decrease in fatigue, weakness, and gastrointestinal side effects when fasting. Although, fasting did not prevent chemotherapy-induced reductions in tumor volume or tumor markers in patients whose cancer progression could be examined. So here it's suggested that fasting combined with chemotherapy is practical, safe, and has the potential to alleviate chemotherapeutic adverse effects [104]. Moreover, a randomized crossover clinical trial was undertaken in 34 women with breast or ovarian cancer to investigate the impact of short-term fasting on quality of life and chemotherapy side effects [105]. The short--term fasting consisted of a 400 kcal daily calorie intake, mainly from juices and broths, commencing 36-48 hours before the start of chemotherapy and lasting until 24 hours after the end of chemotherapy. The results showed that fasting is well tolerated and appears to improve quality of life and fatigue during chemotherapy [105]. In another study, 13 women with HER2 negative, stage II/III breast cancer who were receiving neo-adjuvant taxotere, adriamycin, and cyclophosphamide (TAC) chemotherapy were randomly assigned to either a 24-hour fast (water only) before and after starting chemotherapy. This study showed that Short-term fasting was well tolerated and minimized the drop in mean erythrocyte and thrombocyte counts 7 days post-chemotherapy [106]. It's noteworthy to mention that levels of γ-H2AX (a marker of DNA damage) were significantly increased 30 min post-chemotherapy in leucocytes in non-fasting patients but not in fasting patients [106]. Similarly, DNA damage in leucocytes was reduced in 20 patients receiving platinum-based chemotherapy (mostly with urothelial, ovarian, or breast cancer) who were randomly assigned to fast for 24, 48, or 72 hours (split as 48 hours pre-chemotherapy and 24 hours post-chemotherapy) [107]. Recently, a clinical trial was conducted assessing the safety and biological effects of cyclic, five--day fasting-mimicking diet (FMD) in combination with standard anticancer therapies. The results have shown that cyclic FMD is a safe, feasible, and low-cost dietary intervention that regulates systemic metabolism and promotes antitumor immunity in cancer patients [108]. Additionally, a study was conducted on 14 healthy subjects (13 males:1 female) who fasted 30 days consecutively for more than 14 hours per day. The results showed that fasting from dawn to sunset is correlated to an anticancer proteomic signature [90].

What makes fasting an important issue, especially in cancer patients, is the safety provided by fasting even when patients are undergoing chemotherapy or any other therapy and this is the common point in all the clinical studies cited previously. This point of view is confirmed also by a recent clinical trial, which proved that fasting during the holy month of Ramadan in colorectal cancer patients receiving chemotherapy is totally safe [109]. Furthermore, several studies have demonstrated that fasting plays a role in increasing chemotherapy tolerability and reducing the toxicity of chemotherapeutic drugs and sensitizing cancer cells to the treatment [110-114]. Fasting during chemotherapy treatment, on the other hand, was far more effective than either alone in delaying the progression of a variety of tumors, including breast cancer and glioma, reducing the number of organs affected by melanoma metastases, and promoting long-term cancer-free survival in up to 40% of mice with neuroblastomas [114]. Also fasting induces a differential stress resistance (DSR) between normal cells and cancer cells [110, 115].

Given that following repeated cycles of treatment, cancer cells known as drug-tolerant persister (DPT) have the ability to develop an acquired resistance against cancer treatment which constitutes a block during the treatment journey [116]. According to Liu *et al.*, ferroptosis, a type of intracellular iron-dependent cell death, could boost the anticancer activity of FMD + chemotherapy and offer a possible therapeutic option to minimize DTP cell-driven tumor relapse and therapy failure in colorectal cancer patients. So fasting combined with ferroptosis inducer treatment inhibits tumor growth and eliminates dormant cells by increasing autophagy [117]. In addition, fasting promotes autophagy which consequently may exert a protective effect by mobilizing autophagic components prior to chemo-induction. On the genetic level it was demonstrated that fasting could considerably decrease p21, p16, and p53 expression at a later point in time [118].

Accumulating evidence suggests that the antineoplastic impact of several chemotherapeutic drugs is dependent not only on their cytotoxic effects but also on their capacity to restore immune surveillance after triggering immunogenic cell death (ICD) in cancer cells [119]. Actually, certain chemotherapeutics that stimulate ER stress, like mitoxantrone and anthracyclines such as doxorubicin, increase the expression of calreticulin on the cell membrane, which enhances the engulfment of apoptotic bodies by antigen-presenting cells [120]. Another characteristic of ICD is the liberation of danger-associated molecules (DAPMPs) such as ATP, several heat shock proteins, and signaling molecules (cytokines such as IL-1α) [121]. As a result the pro-inflammatory condition triggered by these DAMPs and inflammatory mediators, boosts dendritic cell maturation and subsequent activation of CD4+ and CD8+ T--cells [121].

Autophagy has been found to increase the immunogenicity of dying tumor cells by secreting HMGB1 [122]. Likewise autophagy has been demonstrated to have an important role in mediating ICD by releasing ATP before apoptosis [123]. This suggests that activating the autophagic mechanism, by fasting, for example, before the administration of chemotherapy drugs known to induce ICD may improve their therapeutic efficacy. Remarkably, new data indicate that this may be the case. Fasting (48 hours) or administration of agents known to upregulate autophagy (hydroxycitrate) enhances the anticancer properties of mitoxantrone and oxaliplatin, an effect that was not observed when cancer cells were implanted in immune-compromised mice or when the critical autophagic gene Atg5 was silenced [124]. So, the statement that fasting increases ICD reveals new mechanisms by which fasting may improve chemotherapeutic efficacy. Because autophagy has a role in the secretion of other ICD agents [125].

Moreover, autophagy plays a crucial role in epitope expression. As we know typically that MHC II epitopes are derived from exogenous (phagocytosed) sources and MHC I from endogenous sources has been augmented by evidence that phagocytosed particles can be expressed on MHC I [126], and contrarily that endogenous epitopes can be expressed by MHC II [127]. Since autophagy has a well-recognized involvement in the expression of epitopes by MHC II [128], new data has implicated autophagy in the expression of epitopes by MHC I [129]. Fasting-induced autophagy may improve the presentation of cytosolic epitopes by providing a steady source of cytosolic proteins that fuse with MHC II loading compartments [128]. Autophagy, induced *in vitro* by fasting, increases the expression of intracellular proteins on MHC II, lending support to this viewpoint [130]. Fasting for a short period of time has also been found to boost the response of mucosal-derived B lymphocytes to an orally administered influenza vaccination [131]. So upregulating autophagy prior to chemotherapy may improve immunization against tumor antigens in the same way as autophagy induction improves vaccine effectiveness. Although autophagy has been related to both procarcinogenic and anticarcinogenic processes, as it regulates oncogenes as well as tumor-suppressor genes [2, 132-135]. It has been proposed that autophagy dysregulation may contribute to cancer [136, 137] *via* a complicated set of pathways that allow tumor cells to survive periods of stress, such as food restriction [138]. But interestingly fasting has been demonstrated to promote autophagy in mammals, and this autophagy-induced autophagy may protect normal cells from malignant transformation [139].

8. FASTING AND COVID-19

The global COVID-19 (SARS-CoV-2 infection) pandemic that ravaged the world has been a serious health concern over the past 3 years. This outbreak of COVID-19 has killed over 5 million people, according to WHO [140]. The coronavirus causing severe acute respiratory syndrome (SARS-CoV-2) has raised a great interest in human immunology and many vaccines have been developed to fight the disease. Despite vaccine deployment, there is no end in sight as SARS-CoV-2 mutates and becomes more virulent. Since the beginning of the pandemic, a variety of therapeutic medications have emerged, with current treatments including, but not limited to, antivirals, immunomodulators (*e.g.*, corticosteroids, biologics), anticoagulants, and complement inhibitors [141], besides some preventative measures like wearing a medical mask, social distancing, washing hands frequently, *etc* [142]. In addition to these precautionary measures, IF and time-restricted eating have been suggested as feasible lifestyle changes to boost the immune system during the COVID-19 pandemic [143]. One of the most common features of severe COVID-19 patients is the systemic hyper-inflammation, described as cytokine storm (144). This inflammatory storm is distinguished by a rapid increase in the inflammatory cytokines interleukin IL-6, IL-1β, tumor necrosis factor (TNF-α) and interferon (IFN-γ) [144, 145]. It's known that an imbalance in the production of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1, IFNγ type I and II, and IL-10 contributes to immunological dysfunction and facilitates inflammation of target tissues [146]. On another hand, and, as we've discussed above about the effect of fasting on human immune system and how fasting contributes to a reduction in pro-inflammatory cytokines and the serum levels of the pro-inflammatory cytokines IL-6, IL-1, and TNF-α were considerably lower ($P<0.05$) throughout Ramadan than before Ramadan or after RIF was stopped. Furthermore, the number of immune cells decreased considerably during Ramadan but remained within normal reference levels [88].

From another angle, there is β-hydroxybutyrate (B-HB), a ketone body, the product of β-oxidation of free fatty acids located in the liver, which is considered a fuel source during the fasting period and absorbed by peripheral tissues as an alternative energy source. BHB is not just an energy source, but also a multifunctional molecule with cellular signaling capabilities that has direct effects on immune cells [147]. BHB has been linked to strengthen T cell performance in humans [148]. A recent study found that decreased BHB production is associated with impaired CD4+ T cell function in patients with severe COVID-19 and that BHB supplementation or oral administration of ketone esters improves CD4+ T cell survival and their capacity to produce IFN-γ, thus enhancing the antiviral immune response [149]. This difference between fasting condition and non-fasting condition is that CD4+ T cells from COVID-19-associated acute respiratory distress syndrome (ARDS) patients express PD-1 (in many clinical contexts, PD-1 is linked to T cell exhaustion or dysfunction [150] and are physiologically biased toward glycolysis. As the primary carbon source, glucose is diverted into the generation of lactate and pentose phosphate pathway intermediates rather than the TCA cycle, resulting in reduced amino acid synthesis and compromised IFN production capacity. While during fasting, BHB is synthesized in the liver from fatty acids and serves as an alternative carbon source to fuel the TCA cycle, resulting in increased mitochondrial OXPHOS and decreased glycolysis, enhancing cellular capacity to produce IFN-γ and boosting antiviral immune response [151]. As PD-1 is associated with T cell exhaustion or dysfunction in many clinical settings [150].

9. EFFECT OF FASTING ON NERVOUS SYSTEM

The nervous system is a complex network of specialized cells and tissues that coordinates and regulates the functions of the human body. It is crucial to the functioning of systems like homeostasis, motor control, sensory perception, and brain function [152]. The nervous system consists of two main components: the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS), composed of nerves and ganglia outside the CNS. The CNS serves as the control center, including and processing data from the PNS to produce the necessary responses. The CNS can communicate with different organs, muscles, and tissues thanks to the PNS, which links the CNS to the rest of the body [153].

As we mentioned before, scientific investigations have shed light on the potential effects of fasting on different biological systems within the body, including the nervous system. The nervous system is one of the most important and vital systems in the human body, it is a complex network of cells and tissues that controls and coordinates bodily functions. By exploring the influence of fasting on the nervous system, we can delve deeper into the fascinating interplay between nutrition and brain function (Fig. **4**).

A variety of adaptive reactions, including the induction of cellular repair and renewal mechanisms, are triggered by the metabolic switching between fasting and eating states during IF [154]. IF has been shown to enhance synaptic plasticity. This refers to the ability of neurons to strengthen or weaken connections with one another which is an important neurophysiological process involved in brain networks development [155]. However, the length and timing of fasting periods may affect how much neuroplastic change occurs. The expression of heat shock proteins (HSP), which can defend neurons from harm, is one of the cellular stress responses that IF triggers [154]. Moreover, IF boosts the production of neurotrophic factors such brain-derived neurotrophic factor (BDNF), which helps neurons develop and survive [154]. To maintain synaptic integrity and plasticity, autophagy is required. And fortunately, brief fasting triggers a process known as autophagy, which includes the breakdown and recycling of cellular components, causing the elimination of damaged organelles and proteins. This enhances brain health and might support neuroplasticity [156]. Also, fasting promotes the expression of genes involved in autophagy

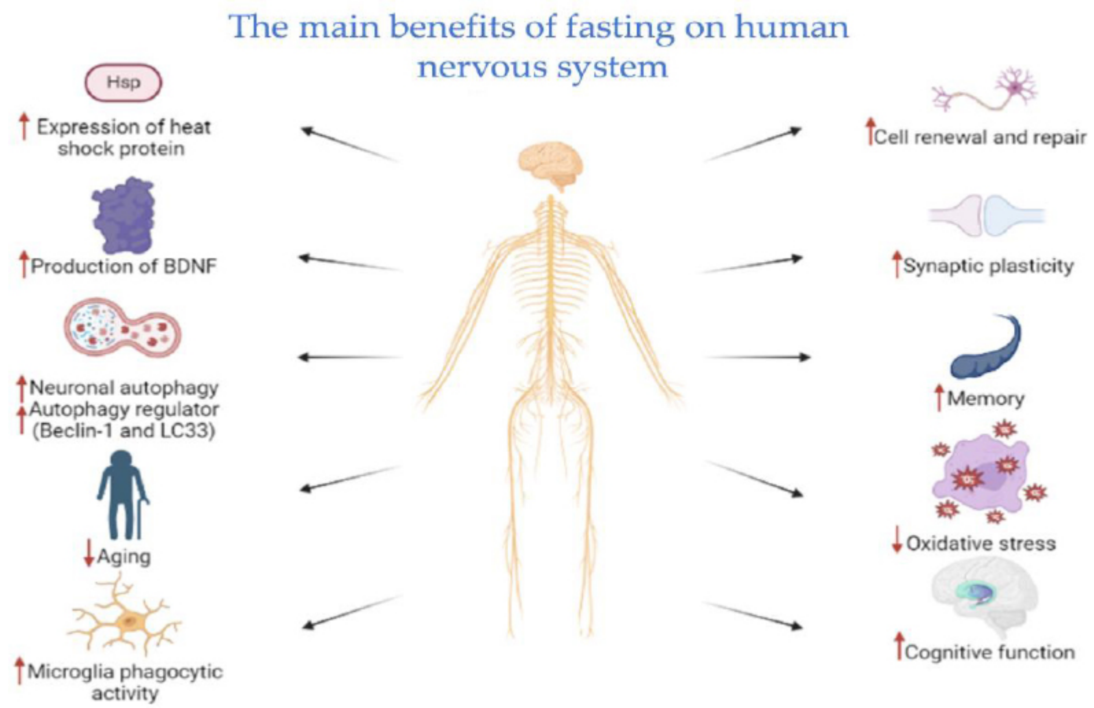

Fig. (4). The impact of fasting on the nervous system. Created with BioRender.com. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

in the brain. Fasting-induced increased autophagy may shield neurons against aging- and disease-related deterioration. In preclinical studies, autophagy-induced fasting has been shown to improve neuronal function. The AMP-activated protein kinase (AMPK) pathway is one of the cellular signaling pathways that can be triggered by fasting and controls autophagy [156]. It is shown that fasting increases the expression of brain-specific autophagy regulators like Beclin-1 and LC3 in areas of the brain linked to synaptic plasticity. So fasting-induced autophagy controls synaptic protein and organelle turnover, enhancing synaptic plasticity and the health of neurons [157].

Moreover, studies on animals show that IF stimulates the production of new neurons in the hippocampus, an area of the brain essential for memory and learning. Hence IF can promote memory development and consolidation, boost cognitive function, and guard against neurodegenerative disorders [154].

Furthermore, in a study conducted on rats, IF has been shown to reduce oxidative stress and age-related alterations in the rat hippocampus. Administration of lipopolysaccharide (LPS) causes oxidative stress and reduces Na, K-ATPase activity in the hippocampus. Interestingly, IF has been found to prevent the Na, K-ATPase activity decrease brought on by LPS, which is crucial for preserving synaptic plasticity and neuronal function [158].

A mitochondrial enzyme called SIRT3 is essential for controlling how neurons respond to different stresses, including exercise and changes in metabolism. Different proteins involved in the operation and plasticity of neurons are controlled by SIRT3's acetylation levels. SIRT3 activation brought on by fasting offers neuroprotection from excitotoxicity and metabolic stress [159].

Microglia undergo metabolic reprogramming as a result of fasting. Fasting-induced metabolic alterations in microglia boost their inflammatory reactions to microbial activation. The improvement of microglial immunity caused by fasting may aid in the healing of neuroinflammation [160]. According to a study, fasting increases neural resilience while reducing microglia activation and the release of pro-inflammatory cytokines [161]. In fact, the increase of fatty acid oxidation and glycolysis is a part of metabolic reprogramming. Microglia expresses more antimicrobial and pro-inflammatory genes while fasting. The metabolic alterations brought on by fasting enhance microglia's phagocytic activity. Moreover, fasting improves the microglial response to the bacterial stimulant lipopolysaccharide (LPS) [160].

Additionally, fasting encourages the development of ketone bodies, an alternative energy source, and strengthens the brain's defenses against oxidative stress and inflammation [162]. All of these outcomes open up a window for developing safe effective strategies that could help in treating some brain disorders by fasting.

10. OTHER BENEFITS OF FASTING

Having explored the effects of fasting on various body's physiological systems and mechanisms such as the cardiovascular, immune, nervous, diabetes, obesity and cancer, it is evident that fasting significantly influences vital physiological processes and prolongs the lifespan [163-165]. However, the intricate relationship between fasting and the human body extends beyond the realms of the systems and mechanisms alone. To gain a comprehensive understanding of the broader implications of fasting, it becomes imperative to delve into the effects on distinct systems that have received less attention, like kidney diseases, and genital and hormonal changes.

Starting with patients suffering from chronic kidney disease (CKD), a study has shown that people with CKD grades 2-4 could fast during Ramadan along with no noticeable deterioration of their renal function and a satisfactory level of safety and along with the consultation of their physicians [166], but it is noteworthy to mention that there is a shortage of literature on this area, and there are no guidelines to help clinicians advise their patients about the risks of Ramadan fasting on their renal function [167]. In addition to another study about urinary tract stones, when compared to non-fasting months, fasting throughout Ramadan does not raise the risk of getting urinary tract stones, especially when the temperature is not very high because warmer temperature might increase the likelihood of dehydration and a decrease in urine volume in patients, exposing them to developing of urinary stones [168]. However, recent research from preclinical experiments implies that more tightly defined dietary regimens, including caloric restriction and IF, hold promise to slow disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD), which is characterized by the progressive growth of renal cysts, leading to the loss of functional nephrons, and the outcomes of currently underway human clinical studies are eagerly anticipated [169]. Fasting was found to be a potent nutritional strategy to limit oxidative stress and mitochondrial dysfunction in early acute kidney injury, as well as to promote long-term protection against fibrosis by increasing antioxidant protection independently of the NF-E2-related factor 2 (Nrf2) and by maintaining mitochondrial morphology and function in an experimental rat model study published in May 2019 [170, 171]. Another study talking about the same disease demonstrated that fasting also reduces inflammation and endoplasmic reticulum stress, as well as down-regulation of the mechanistic target of rapamycin (mTOR) and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathways in the fibrotic kidney [171].

Considering the importance of fasting on other points, a study published in 2020 by Liang *et al.* reported that patients following an organic diet or IF were considerably more unlikely to have erectile dysfunction (ED). As a result, this was the first study to suggest that an organic diet and IF are protective against ED [172]. So, these findings merit additional investigation to better understand and assume that IF is associated with improved erectile function and to understand other beneficial effects on the genital system. Another research conducted on diet and gut microbiome interactions in gynecologic cancer showed that time-controlled (intermittent) fasting promotes metabolic reprogramming and can sensitize cancer cells to chemotherapy by decreasing IGF-1 signaling, increasing reactive oxygen species, and inducing DNA damage [173]. Research investigations on the effects of dietary interventions, such as IF, on chemotherapy response and the composition of the gut microbiome in patients with advanced gynecologic malignancy are highly desirable and have the potential to drastically modify practice results in a positive way [174]. Studying the effect of IF on reproductive hormone levels, a study has shown that fasting may be a useful method for treating hyperandrogenism in females with polycystic ovarian syndrome (PCOS) by improving menstruation and fertility [175, 176]. In addition to these studies, another one demonstrated that TRF has the potential to have benefits on anovulatory PCOS patients in losing weight through lowering body fat, improving menstruation, hyperandrogenemia, insulin resistance, and chronic inflammation [177]. The fact that fasting intermittently may modify simultaneously the level and frequency of hormone secretion in hormonal circadian rhythms, recommendations about whether or not to undergo IF ought to take into consideration the potential negative consequences versus beneficial consequences associated with individual health conditions (Table **2**) [178].

Table 2. A table showing some positive and negative effects of IF.

Effect	Positive Effects	Negative Effects	Reference
Weight Loss	Reduced calorie intake leads to weight loss	Potential for overeating during eating windows	[179]
Insulin Sensitivity	Improved insulin sensitivity	Potential for hypoglycemia during fasting	[180]
Blood Sugar Control	Better blood sugar control	Risk of blood sugar spikes after breaking fast	[181]
Brain Function	Enhanced brain function and neuroprotection	Potential for cognitive decline during fasting	[154]
Longevity	Potential for increased lifespan	Requires careful planning to avoid nutrient deficiencies	[182]

Knowing the importance of good liver function, a study in 2021 showed that Ramadan diurnal intermittent fasting (RDIF) triggers significant but small (aspartate aminotransferase-AST, alkaline phosphatase-ALP, bilirubin-BLU) to medium (gamma-glutamyl transferase-GGT) beneficial variations on the liver function tests (LFT), and could provide a temporary, short-term defense towards fatty liver disease in individuals who are in good health [183]. Furthermore, nonalcoholic fatty liver disease (NAFLD) is a severe global medical issue, linked to metabolic diseases such as central obesity, dyslipidaemia, hypertension, hyperglycemia, and persistent abnormalities in liver function tests [184]. Hence disease prevention and management are essential. Ebrahimi *et al.* conducted a study on individuals suffering from NAFLD to investigate the effects of Ramadan Fasting (RF) on liver function, Visceral Adiposity Index (VAI), and Atherogenic Index of Plasma (AIP). The current research reported that RF improved hepatic steatosis in NAFLD patients, suggesting that it may be effective in the treatment of NAFLD [185].

CONCLUSION

To sum up, fasting has a significant impact on various body systems, highlighting its potential benefits for overall health and well-being. Specifically, concerning the cardiovascular system, fasting appears to promote cardiovascular health by reducing blood pressure, improving lipid profiles, and enhancing heart function. In relation to the nervous system, fasting has been found to enhance brain function, promote neuroplasticity, and potentially protect against neurodegenerative diseases. Additionally, evidence suggests that fasting can modulate the immune system, enhancing immune responses, reducing inflammation, and promoting immune cell regeneration. When it comes to cancer, fasting has shown promising effects in complementing cancer treatment by enhancing chemotherapy efficiency, reducing side effects, and potentially inhibiting tumor growth through various mechanisms. The COVID-19 pandemic has shed light on the potential benefits of fasting in strengthening the immune system and improving overall health, potentially reducing the severity of viral infections. In terms of the RAS, fasting has been observed to regulate blood pressure, improve vascular function, and potentially reduce the risk of developing hypertension and cardiovascular diseases. Fasting also shows promise in managing diabetes and obesity, as it can improve insulin sensitivity, regulate blood glucose levels, and promote weight loss. Lastly, autophagy, a cellular self-cleaning process, is enhanced during fasting periods, which can help in cellular rejuvenation, removal of damaged molecules, and potentially anti-aging effects. However, further research is still needed to better understand the specific mechanisms underlying these effects and to optimize fasting protocols for various health conditions.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
IF	=	Intermittent Fasting
T2DM	=	Type 2 Diabetes Mellitus

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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